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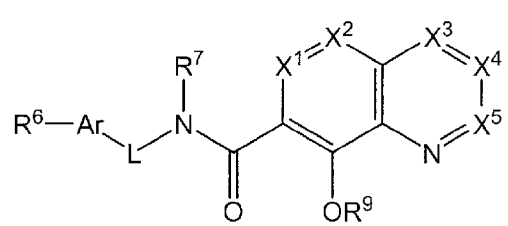
(54) **Title:** AZA-QUINOLINOL PHOSPHONATE INTEGRASE INHIBITOR COMPOUNDS



(I)

(57) **Abstract:** Aza-quinolinol phosphonate compounds and methods for inhibition of HIV-integrase are disclosed. Formula (I). Ar is aryl or heteroaryl connecting R^6 to L. L is a bond or a linker connecting a ring atom of Ar to N. The ring atoms, X^1-X^5 may be N, substituted nitrogen, or substituted carbon, and form rings. The compounds include at least one phosphonate group covalently attached at any site.

AZA-QUINOLINOL PHOSPHONATE INTEGRASE INHIBITOR COMPOUNDS

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity and more specifically with HIV-integrase inhibitory properties.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. A virally encoded integrase protein mediates specific incorporation and integration of viral DNA into the host genome. Integration is essential for viral replication. Accordingly, inhibition of HIV integrase is an important therapeutic pursuit for treatment of HIV infection and related diseases.

Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, etal *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001). There is a need for new agents directed against alternate sites in the viral life cycle. Integrase has emerged as an attractive target, because it is necessary for stable infection and homologous enzymes are lacking in the human host (LaFemina, etal *J. Virol.* (1992) 66:7414-7419). The function of integrase is to catalyze integration of proviral DNA, resulting from the reverse transcription of viral RNA, into the host genome, by a stepwise fashion of endonucleolytic processing of proviral DNA within a cytoplasmic preintegration complex (termed 3'-processing or "3'-P") with specific DNA sequences at the end of the HIV-1 long terminal repeat (LTR) regions, followed by translocation of the complex into the nuclear compartment where integration of 3'-processed

proviral DNA into host DNA occurs in a "strand transfer" (ST) reaction (Hazuda, etal *Science* (2000) 287:646-650; Katzman, etal *Adv. Virus Res.* (1999) 52:371-395; Asante-Applah, etal *Adv. Virus Res.* (1999) 52:351-369). Although numerous agents potently inhibit 3'-P and ST in extracellular assays that employ recombinant integrase and viral long-terminal-repeat oligonucleotide sequences, often such inhibitors lack inhibitory potency when assayed using fully assembled preintegration complexes or fail to show antiviral effects against HIV-infected cells (Pommier, etal *Adv. Virus Res.* (1999) 52:427-458; Farnet, etal *Proc. Natl. Acad. Sci. U.S.A.* (1996) 93:9742-9747; Pommier, etal *Antiviral Res.* (2000) 47:139-148.

Certain HIV integrase inhibitors have been disclosed which block integration in extracellular assays and exhibit good antiviral effects against HIV-infected cells (Anthony, etal WO 02/30426; Anthony, etal WO 02/30930; Anthony, etal WO 02/30931; WO 02/055079; Zhuang, etal WO 02/36734; US 6395743; US 6245806; US 6271402; Fujishita, etal WO 00/039086; Uenaka etal WO 00/075122; Selnick, etal WO 99/62513; Young, etal WO 99/62520; Payne, etal WO 01/00578; Jing, etal *Biochemistry* (2002) 41:5397-5403; Pais, etal *Jour. Med. Chem.* (2002) 45:3184-94; Goldgur, etal *Proc. Natl. Acad. Sci. U.S.A.* (1999) 96:13040-13043; Espeseth, etal *Proc. Natl. Acad. Sci. U.S.A.* (2000) 97:11244-11249).

HIV integrase inhibitory compounds with improved antiviral and pharmacokinetic properties are desirable, including enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo* (Nair, V. "HIV integrase as a target for antiviral chemotherapy" *Reviews in Medical Virology* (2002) 12(3):179-193; Young (2001) Current Opinion in Drug Discovery & Development, Vol. 4, No. 4, 402-410; Neamati (2002) Expert. Opin. Ther. Patents Vol. 12, No. 5, 709-724). Three-dimensional quantitative structure-activity relationship studies and docking simulations (Buolamwini, etal *Jour. Med. Chem.* (2002) 45:841-852) of conformationally-restrained cinnamoyl-type integrase inhibitors (Artico, etal *Jour. Med. Chem.* (1998) 41:3948-3960) have shown a large contribution of hydrogen-bonding interactions to the inhibitory activity differences among the compounds. Conformationally-constrained hydrogen-bonding functionality such as hydroxyl was correlated with inhibitory activity. Compounds with binding functionality in a pre-organized configuration may possess optimized inhibitory properties against HIV integrase. The prior art does not show or

suggest compounds with integrase binding functionality in a pre-organized conformation or molecular structure. In addition to therapeutic uses, the value of compounds in diagnostic assays for HIV, for use in the preparation of polymers and for use as surfactants, and in other industrial utilities will be readily apparent to those skilled in the art.

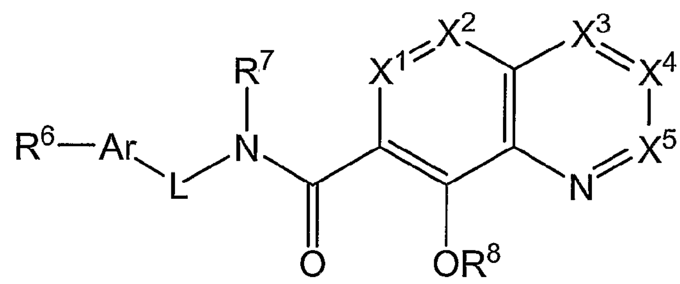
Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods for inhibition of HIV-integrase.

The invention provides a compound having the structure:



or a pharmaceutically acceptable salt thereof, and including enol and tautomeric resonance isomers;

wherein:

X^1 is CR^1, NR, or N;

X^2 is CR^2, NR, or N;

X^3 is CR^3, NR, or N;

X^4 is CR^4, NR, or N;

X^5 is CR^5, NR, or N;

at least one of X^1, X^2, X^3, X^4, and X^5 is NR or N;

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently selected from H, F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1–C_8 alkyl, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-C(=O)OR$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1–C_8 alkoxy ($-OR$), C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety; or when X^1 is CR^1 and when X^2 is CR^2, then CR^1 and CR^2 together may form a ring; when X^3 is CR^3 and when X^4 is CR^4, then CR^3 and CR^4 together may form a ring; or when. X^4 is CR^4 and X^5 is CR^5, then CR^4 and CR^5 together may form a ring; wherein the ring is 5, 6, or 7-membered;

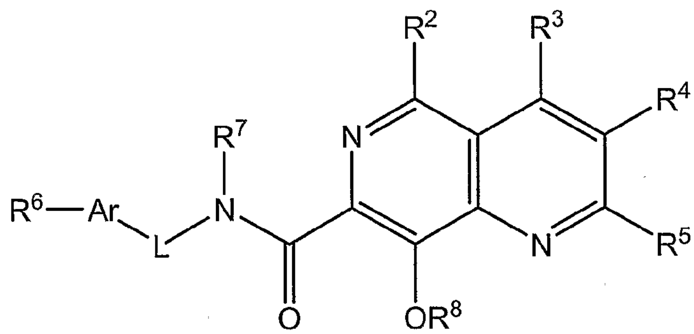
R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

L is selected from a bond, O, S, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6; and

Ar is covalently attached to L and to one or more R^6 and Ar is selected from C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

where at least one of R, R^1, R^2, R^3, R^4, R^5, R^6, $R^7$and R^8 comprises a phosphonate group.

The present invention also provides a compound having the formula:



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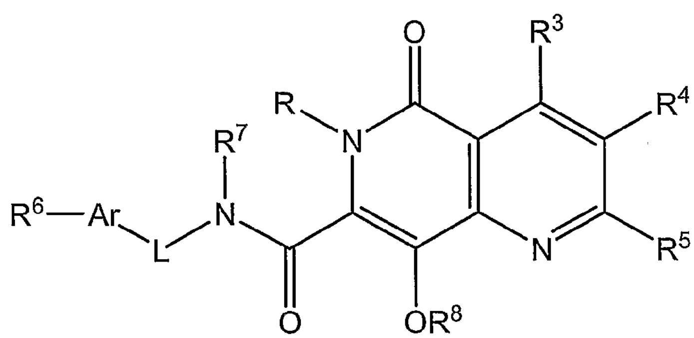
The present invention also provides a compound having the formula:



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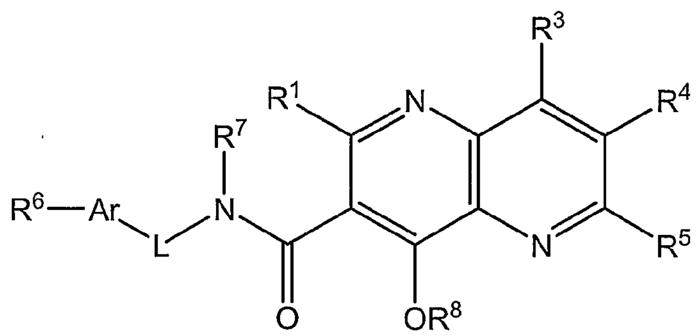

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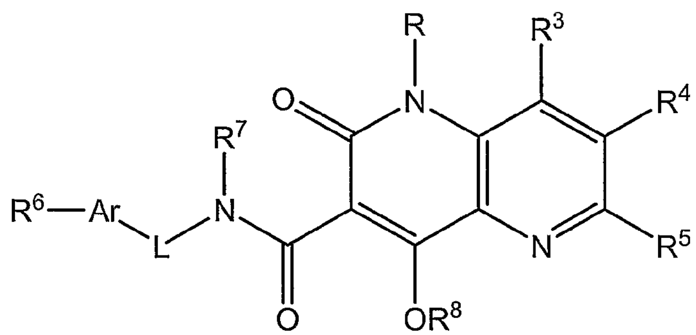

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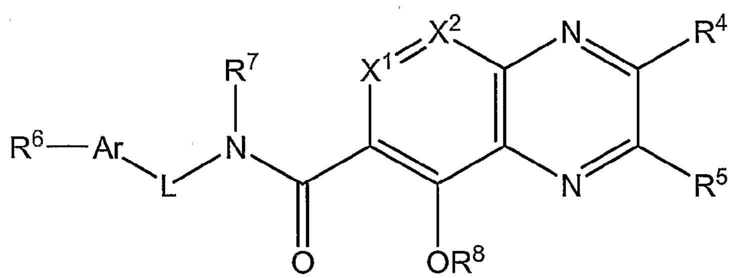

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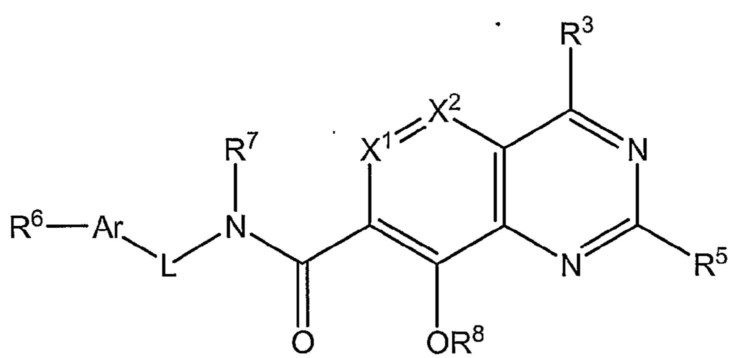

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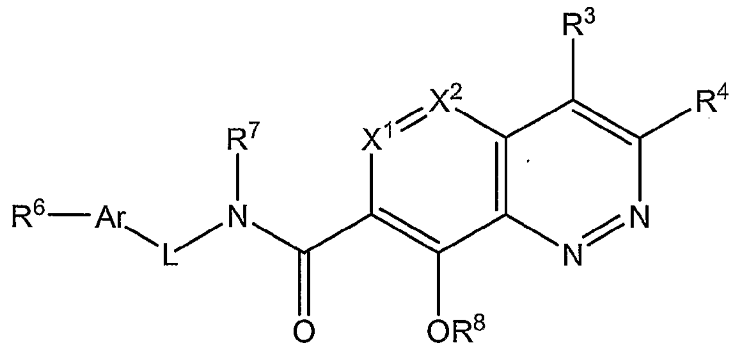

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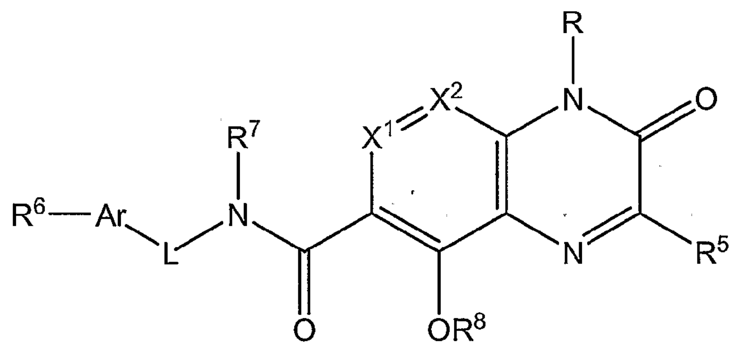

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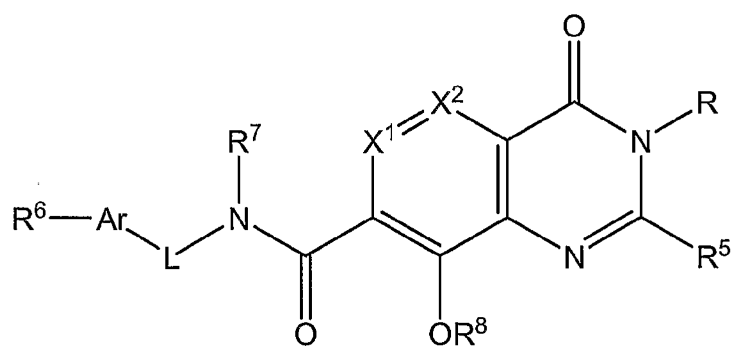

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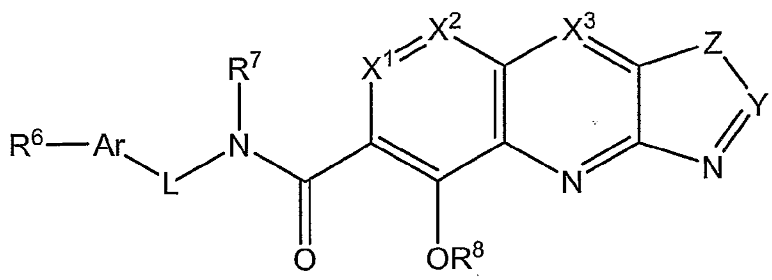


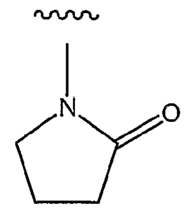
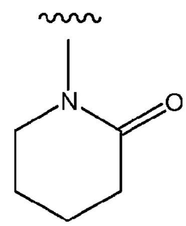
wherein

Y is CR^5, NR or N; and

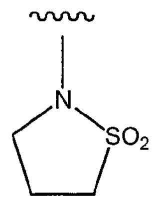
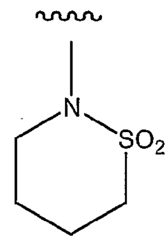
Z is selected from O, S, NR, CR_2, CROR, CROC(=O)R, C(=O), C(=S), CRSR, C(=NR_2), C=CR_2, CR_2–CR_2, CR=CR, NR–CR_2, N=CR, N=N, SO_2–NR, C(=O)CR_2, S(=O)CR_2, SO_2CR_2, C(=O)NR, CR_2–CR_2–CR_2, CR=CR–CR_2, CRC(=O)NR, $CR_2SO_2CR_2$, CR_2SO_2NR, CRC(=S)NR, CR=N–CR_2, CR=N–NR, or N=CR–NR.

Also provided in the present invention are compounds of the above formulae wherein substituted alkylene, substituted alkenylene, substituted alkynylene, substituted aryl, and substituted heteroaryl are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino (–NH_2), ammonium (–NH_3^+), alkylamino, dialkylamino, trialkylammonium, C_1–C_8 alkyl, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, alkylsulfone (–SO_2R), arylsulfone (–SO_2Ar), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide (–SO_2NR_2), alkylsulfoxide (–SOR), ester (–C(=O)OR), amido (–C(=O)NR_2), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido (–N_3), nitro (–NO_2), C_1–C_8 alkoxy (–OR), C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from H, OH, OC(=O)OR, OC(=O)NR_2, OC(=O)R, OSO_2NR_2 (sulfamate), NR_2, $NRSO_2R$, SR, S(O)R, SO_2R or SO_2NR_2 (sulfonamide), lactam having the structures:

 and ,

sultam having the structures:

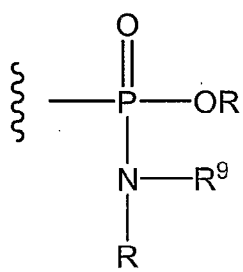
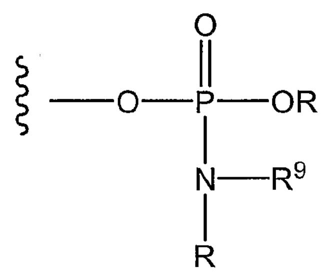
 and ,

and a prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein L is CH_2 and Ar is substituted phenyl.

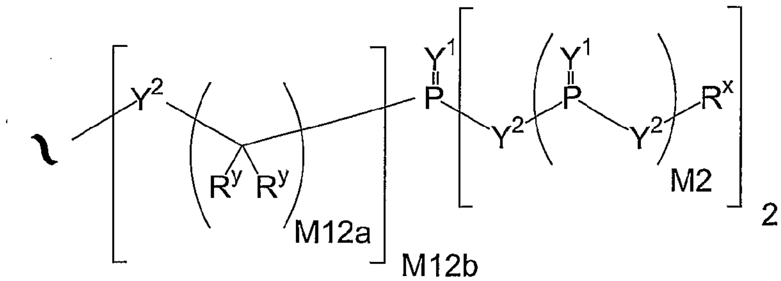
Also provided in the present invention are compounds of the above formulae where L is CH_2 and Ar is 4-fluorophenyl.

Also provided in the present invention are compounds of the above formulae wherein at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 comprise a prodrug moiety selected from the structures:

 and 

wherein R^9 is comprised of an ester, an amide, or a carbamate.

Also provided in the present invention are compounds of the above formulae wherein the phosphonate group has the structure:



wherein:

Y^1 is independently O, S, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), or N(N(R^x)(R^x));

Y^2 is independently a bond, O, N(R^x), N(O)(R^x), N(OR^x), N(O)(OR^x), N(N(R^x)(R^x)), -S(O)- (sulfoxide), -$S(O)_2$- (sulfone), -S- (sulfide), or -S-S- (disulfide);

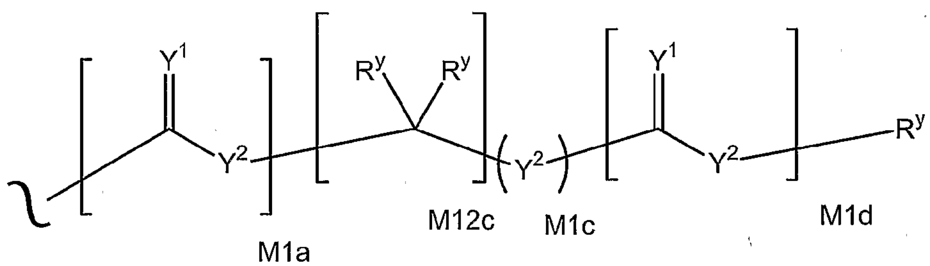
M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

R^y is independently H, alkyl, substituted alkyl, aryl, substituted aryl, or a protecting group, or where taken together at a carbon atom, two vicinal R^y groups form a carbocycle or a heterocycle; and

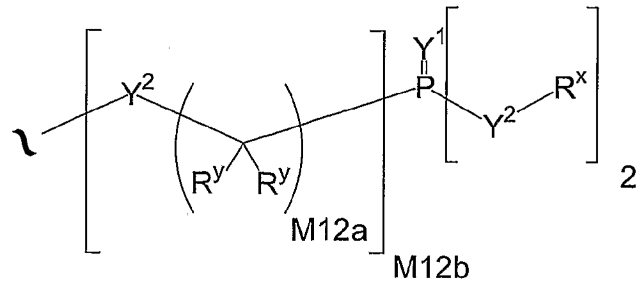
R^x is independently H, alkyl, substituted alkyl, aryl, substituted aryl, or a protecting group, or the formula:



;

where M1a, M1c, and M1d are independently 0 or 1, and M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:



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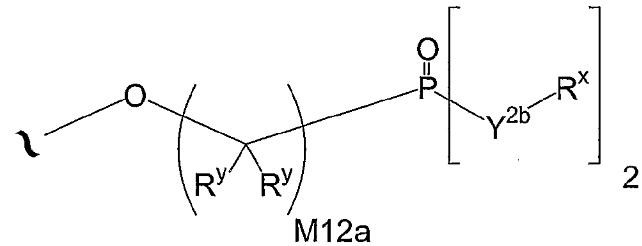
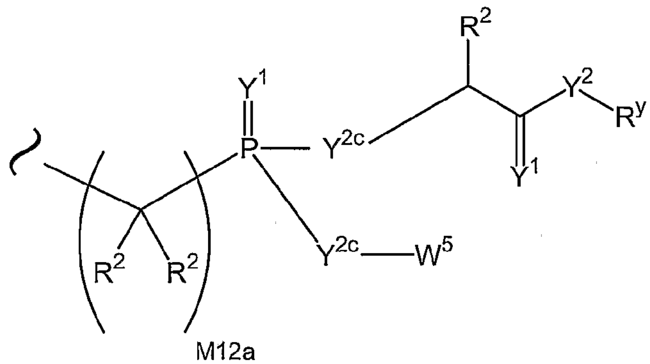


where Y^{2b} is O or $N(R^x)$.

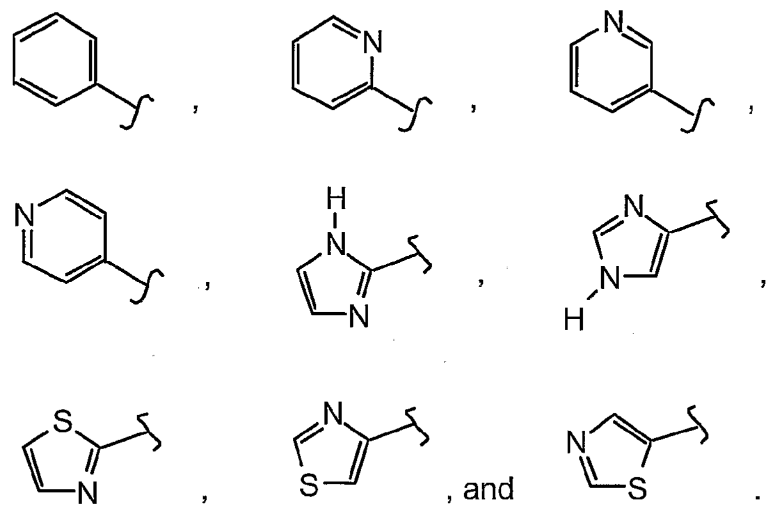
Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:



;

where W^5 is a carbocycle, and Y^{2c} is O, $N(R^y)$ or S.

Also provided in the present invention are compounds of the above formulae wherein W^5 is selected from the structures:



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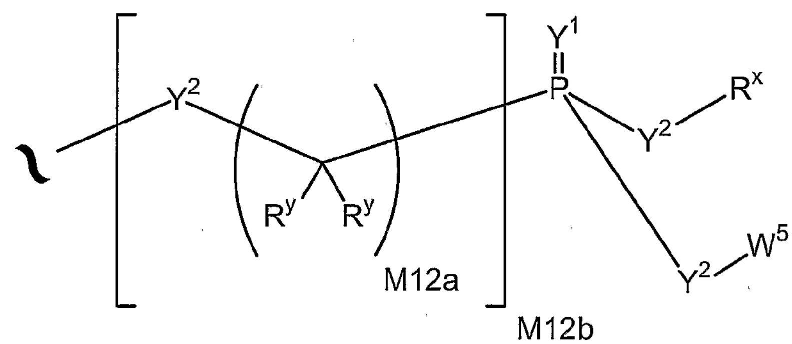

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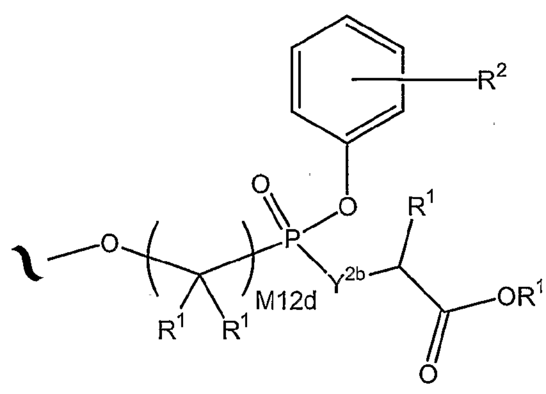
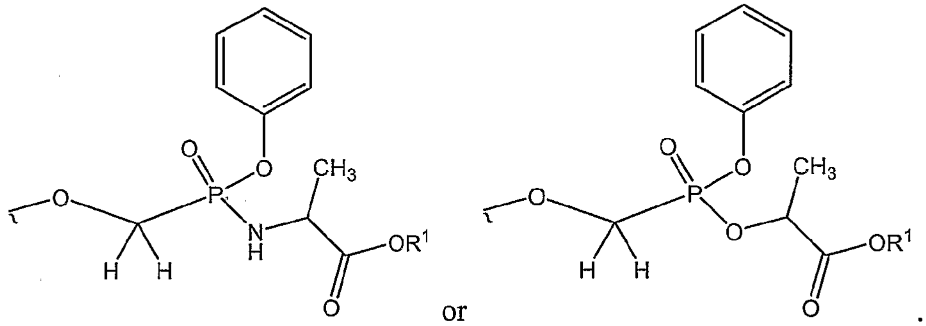
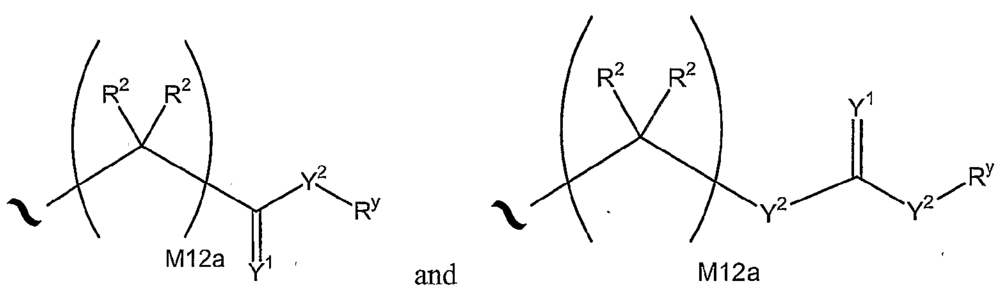


wherein Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; R^1 is H or C_1–C_6 alkyl; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups where R^2 is C_1–C_6 alkyl or substituted alkyl.

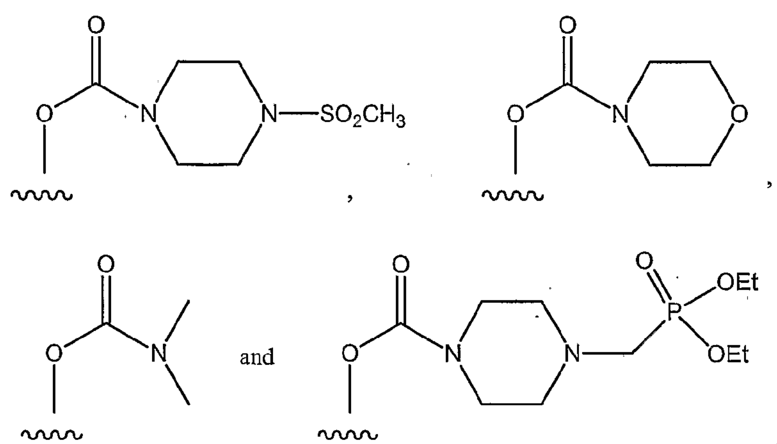
Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:



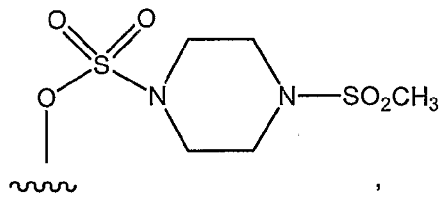
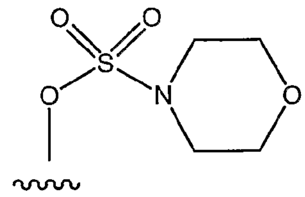
Also provided in the present invention are compounds of the above formulae wherein R^x is selected from the structures:

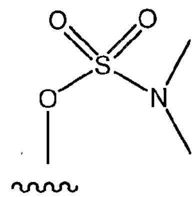
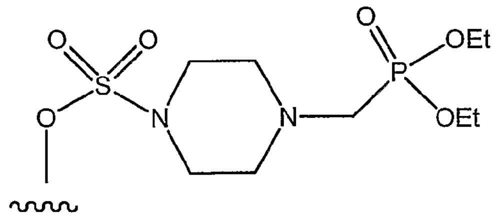


Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from the structures:



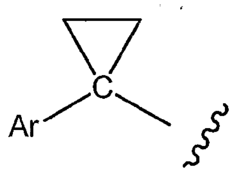
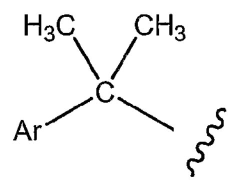
Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from the structures:

,
,

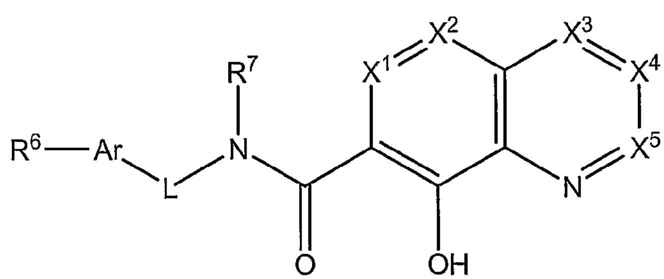
 and .

Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 comprises a phosphonate prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein Ar-L is selected from the structures:

 and .

Also provided in the present invention is a compound of the structure:



or a pharmaceutically acceptable salt thereof, and including enol and tautomeric resonance isomers;

wherein:

X^1 is CR^1, NR, or N;

X^2 is CR^2, NR, or N;

X^3 is CR^3, NR, or N;

X^4 is CR^4, NR, or N;

X^5 is CR^5, NR, or N;

at least one of X^1, X^2, X^3, X^4, and X^5 is NR or N;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from H, F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1-C_8 alkyl, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-C(=O)OR$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1-C_8 alkoxy ($-OR$), C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety; or when X^1 is CR^1 and when X^2 is CR^2, then CR^1 and CR^2 together may form a ring; when X^3 is CR^3 and when X^4 is CR^4, then CR^3 and CR^4 together may form a ring; or when. X^4 is CR^4 and X^5 is CR^5, then CR^4 and CR^5 together may form a ring; wherein the ring is 5, 6, or 7-membered;

R is independently selected from H, C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl;

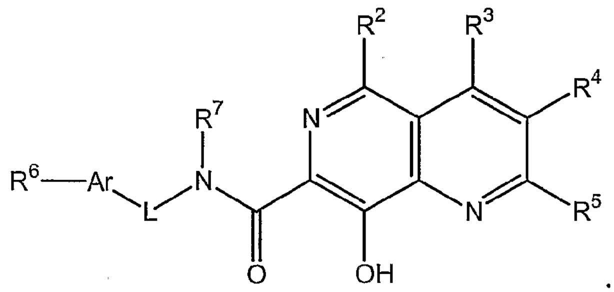
L is selected from a bond, O, S, NR, N–OR, C_1-C_{12} alkylene, C_1-C_{12} substituted alkylene, C_2-C_{12} alkenylene, C_2-C_{12} substituted alkenylene, C_2-C_{12} alkynylene, C_2-C_{12} substituted alkynylene, $C(=O)NH$, $C(=O)$, $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6; and

Ar is covalently attached to L and to one or more R^6 and Ar is selected from C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl;

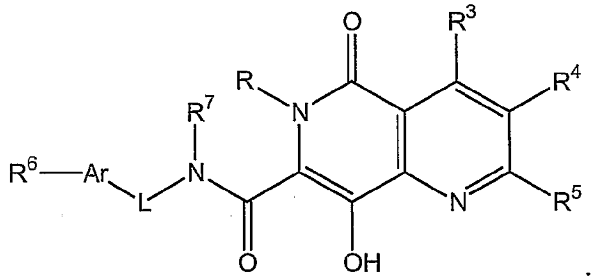
where at least one of R, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 comprises a phosphonate group.

The present invention also provides a compound having the formula:

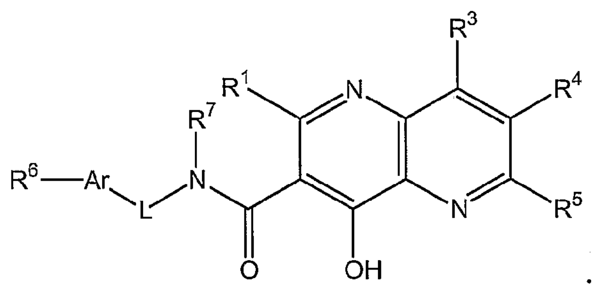
:



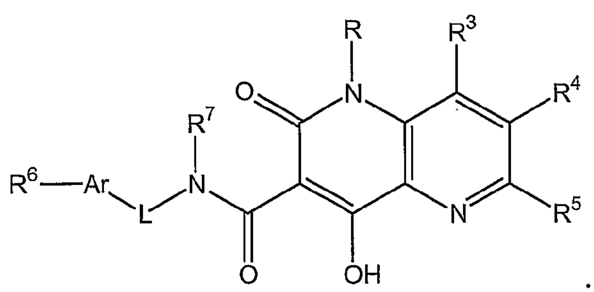
The present invention also provides a compound having the formula:



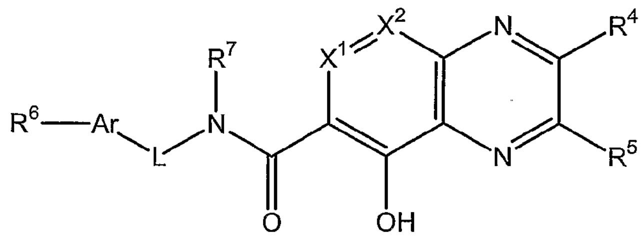
The present invention also provides a compound having the formula:



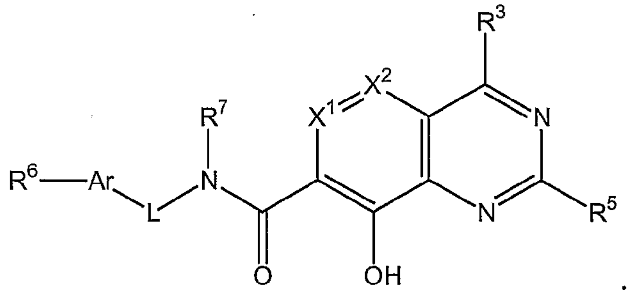
The present invention also provides a compound having the formula:



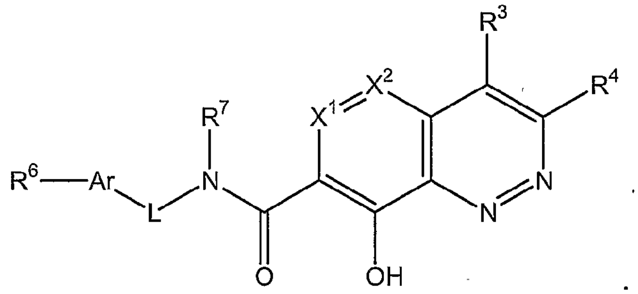
The present invention also provides a compound having the formula:



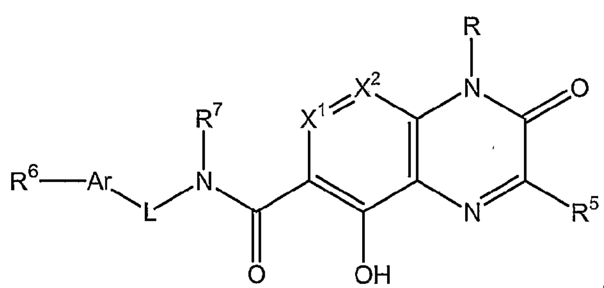
The present invention also provides a compound having the formula:



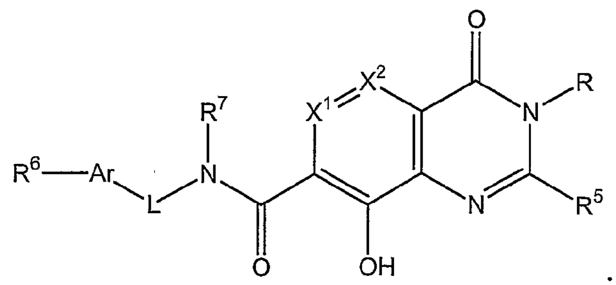
The present invention also provides a compound having the formula:



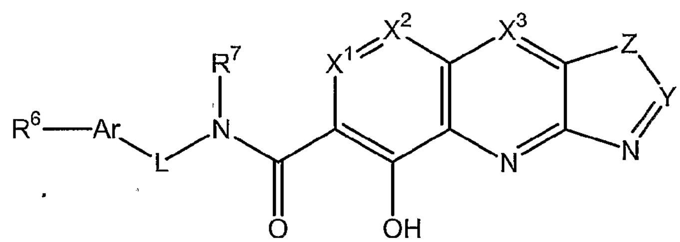
The present invention also provides a compound having the formula:



The present invention also provides a compound having the formula:



The present invention also provides a compound having the formula:



wherein

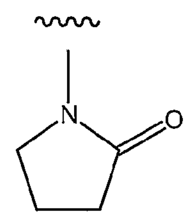
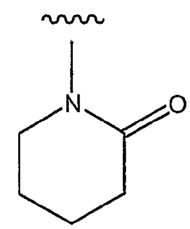
Y is CR^5, NR or N; and

Z is selected from O, S, NR, CR_2, CROR, CROC(=O)R, C(=O), C(=S), CRSR, $C(=NR_2)$, $C=CR_2$, CR_2-CR_2, CR=CR, $NR-CR_2$, N=CR, N=N, SO_2-NR, $C(=O)CR_2$, $S(=O)CR_2$, SO_2CR_2, C(=O)NR, $CR_2-CR_2-CR_2$, $CR=CR-CR_2$, CRC(=O)NR, $CR_2SO_2CR_2$, CR_2SO_2NR, CRC(=S)NR, $CR=N-CR_2$, CR=N–NR, or N=CR–NR.

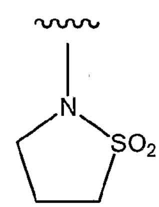
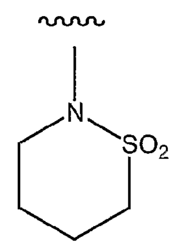
Also provided in the present invention are compounds of the above formulae wherein substituted alkylene, substituted alkyenylene, substituted alkynylene, substituted aryl, and substituted heteroaryl are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1-C_8 alkyl, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), ester (–C(=O)OR), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1-C_8 alkoxy (–OR), C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20}

heteroaryl, and C_2–C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from H, OH, OC(=O)OR, OC(=O)NR_2, OC(=O)R, OSO_2NR_2 (sulfamate), NR_2, $NRSO_2R$, SR, S(O)R, SO_2R or SO_2NR_2 (sulfonamide), lactam having the structures:

 and  ,

sultam having the structures:

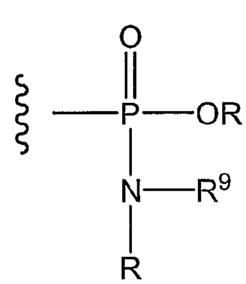
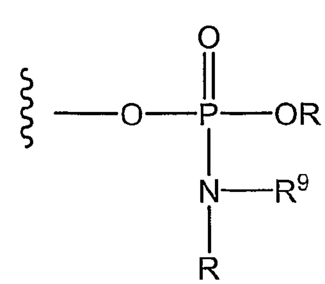
 and  ,

and a prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein L is CH_2 and Ar is substituted phenyl.

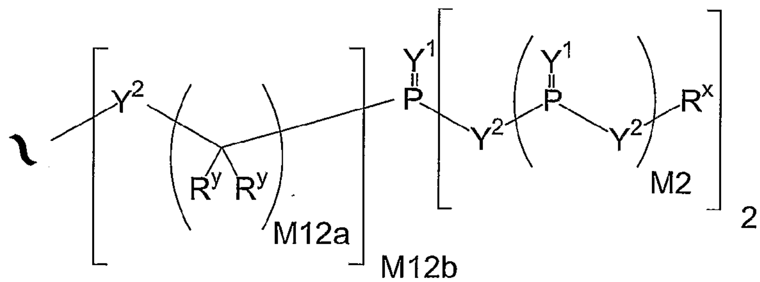
Also provided in the present invention are compounds of the above formulae wherein L is CH_2 and Ar is 4-fluorophenyl.

Also provided in the present invention are compounds of the above formulae wherein at least one of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 comprise a prodrug moiety selected from the structures:

 and 

wherein R^9 is comprised of an ester, an amide, or a carbamate.

Also provided in the present invention are compounds of the above formulae wherein the phosphonate group has the structure:



wherein:

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, -S(O)- (sulfoxide), $-S(O)_2-$ (sulfone), -S- (sulfide), or -S-S- (disulfide);

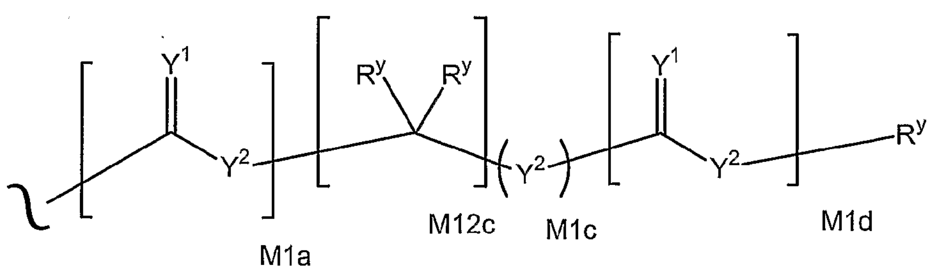
M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

R^y is independently H, alkyl, substituted alkyl, aryl, substituted aryl, or a protecting group, or where taken together at a carbon atom, two vicinal R^y groups form a carbocycle or a heterocycle; and

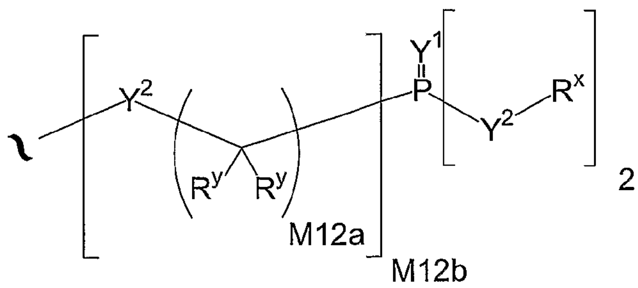
R^x is independently H, alkyl, substituted alkyl, aryl, substituted aryl, or a protecting group, or the formula:



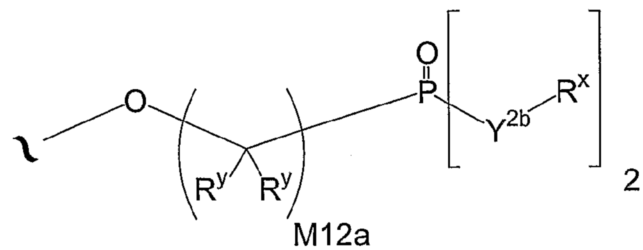
;

where M1a, M1c, and M1d are independently 0 or 1, and M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:

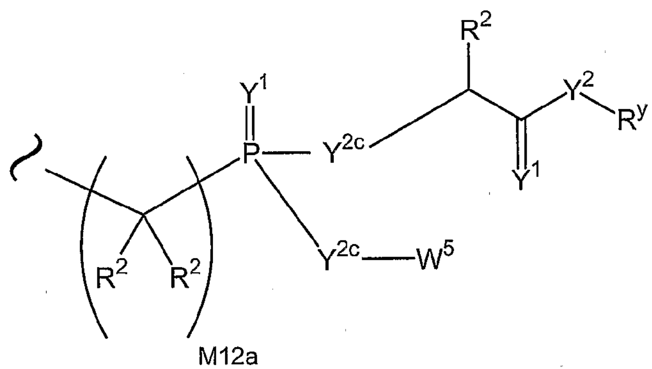


Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:



where Y^{2b} is O or $N(R^x)$.

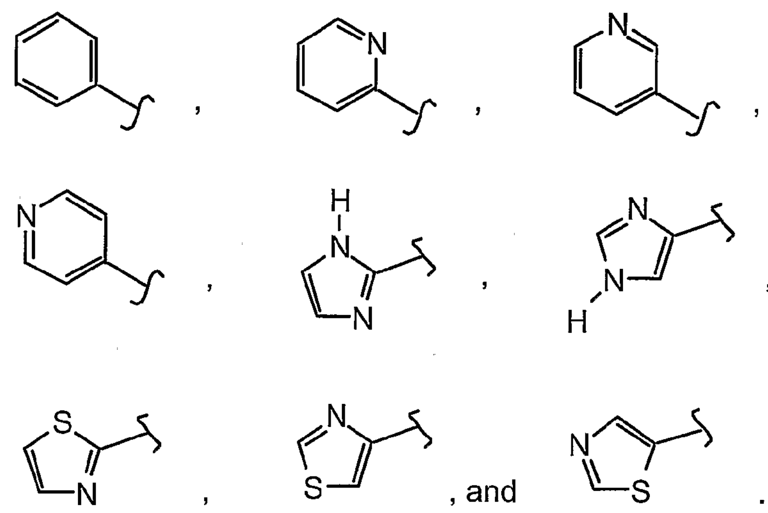
Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:



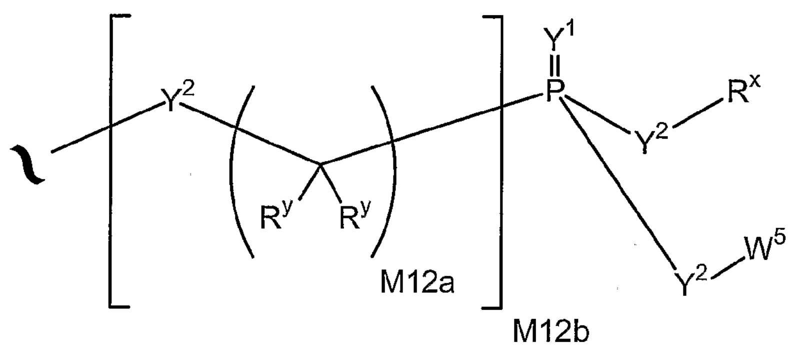
;

where W^5 is a carbocycle, and Y^{2c} is O, $N(R^y)$ or S.

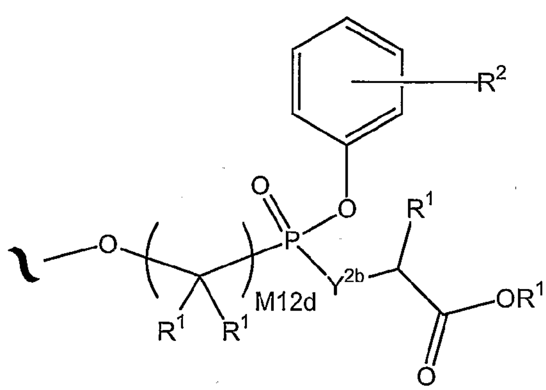
Also provided in the present invention are compounds of the above formulae wherein W^5 is selected from the structures:



Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:

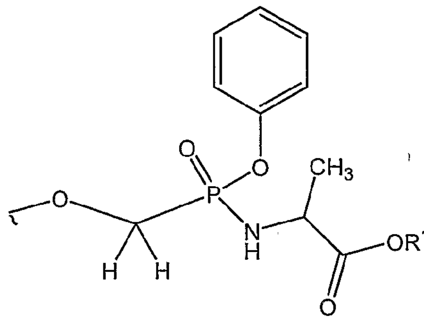


Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:

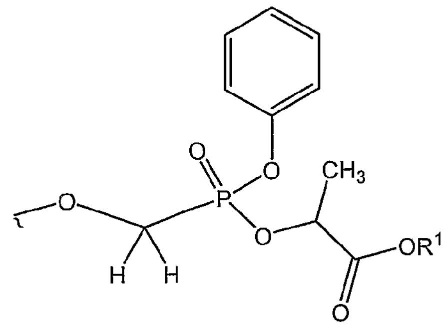


wherein Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; R^1 is H or C_1–C_6 alkyl; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups where R^2 is C_1–C_6 alkyl or substituted alkyl.

Also provided in the present invention are compounds of the above formulae wherein phosphonate group has the structure:

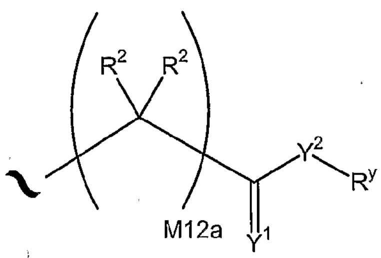


or

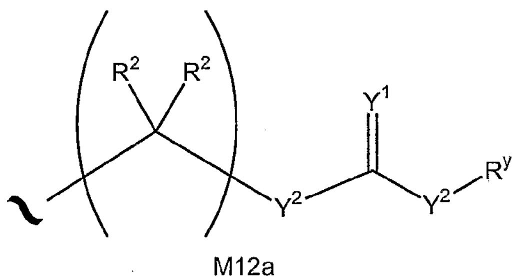


.

Also provided in the present invention are compounds of the above formulae wherein R^x is selected from the structures:

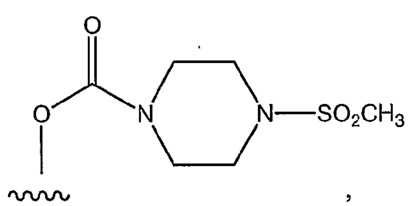


and



.

Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from the structures:



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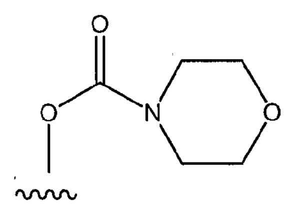

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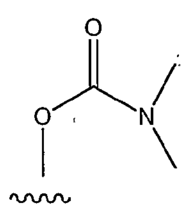

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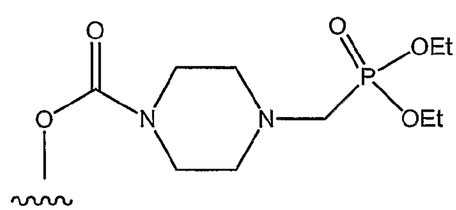
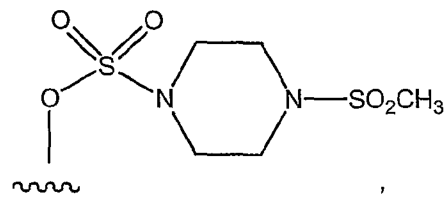
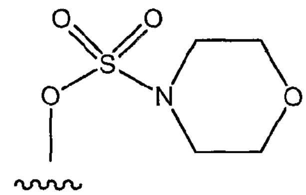
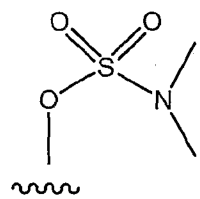
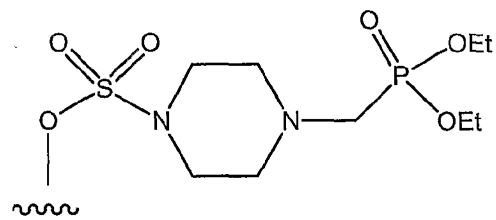


.

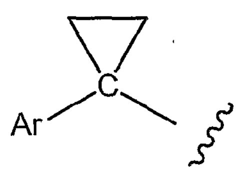
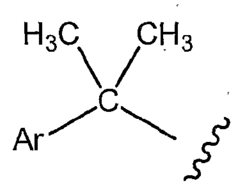
Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 is selected from the structures:

,
,

 and .

Also provided in the present invention are compounds of the above formulae wherein X^2 is CR^2 and R^2 comprises a phosphonate prodrug moiety.

Also provided in the present invention are compounds of the above formulae wherein Ar-L is selected from the structures:

 and .

Also provided in the present invention are pharmaceutical composition comprising a therapeutically effective amount of a compound of any of the above formulae and a pharmaceutically acceptable carrier.

Also provided in the present invention are pharmaceutical composition comprising a therapeutically effective amount of a compound of any the above formulae in combination with a therapeutically effective amount of an AIDS treatment agent selected from:

(1) an AIDS antiviral agent,

(2) an anti-infective agent, and

(3) an immunomodulator.

Also provided in the present invention are pharmaceutical compositions as above wherein the antiviral agent is an HIV protease inhibitor.

Also provided in the present invention are pharmaceutical compositions made by combining the compound of any of the above formulae and a pharmaceutically acceptable carrier.

Also provided in the present invention is a process for making a pharmaceutical composition comprising combining a compound of any of the above formulae and a pharmaceutically acceptable carrier.

Also provided in the present invention is a method of inhibiting HIV integrase, comprising the administration to a mammal in need of such treatment of a therapeutically effective amount of a compound of any of the above formulae.

Also provided in the present invention is a method of treating infection by HIV, or of treating AIDS or ARC, comprising administration to a mammal in need of such treatment of a therapeutically effective amount of a compound of any of the above formulae.

The compounds of the invention include at least one phosphonate group covalently attached at any site.

The invention also includes a pharmaceutical composition comprising an effective amount of a compound selected from the above formulae, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention also includes a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.

The invention also includes a method of inhibiting HIV, comprising administering to a mammal infected with HIV (HIV positive) an amount of a compound of the above formulae, effective to inhibit the growth of said HIV infected cells.

The invention also includes a compound selected from the above formulae for use in medical therapy (preferably for use in treating cancer, e.g. solid tumors), as well as the use of a compound of the above formulae for the manufacture of a medicament useful for the treatment of cancer, e.g. solid tumors.

The invention also includes processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the above formulae are useful to prepare other compounds of the above formulae.

In another aspect of the invention, the activity of HIV integrase is inhibited by a

method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

Another aspect of the invention provides a method for inhibiting the activity of HIV integrase comprising the step of contacting a sample suspected of containing HIV virus with the composition embodiments of the invention.

In other aspects, novel methods for the synthesis, analysis, separation, isolation, crystallization, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying descriptions, structure and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

The terms "phosphonate" and "phosphonate group" mean a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, and nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, phosphondiamidate, and phosphonthioate functional groups.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Pharmaceutically acceptable prodrug" refers to a compound that is metabolized in the host, for example hydrolyzed or oxidized, by either enzymatic action or by general acid or base solvolysis, to form an active ingredient. Typical examples of prodrugs of the compounds of the invention have biologically labile protecting groups on a functional moiety of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, esterified, deesterified, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated, photolyzed, hydrolyzed, or other functional group change or conversion involving forming or breaking chemical bonds on the prodrug.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A "prodrug" is thus a covalently modified analog of a therapeutically-active compound.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl or C_6–C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar etal (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphonate group. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC)

$-CH_2OC(=O)OC(CH_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert etal (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell etal (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook etal WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier etal WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech etal (1993) *Antiviral Res.*, 22: 155-174; Benzaria etal (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion etal, US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain

functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically

acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl ($-CH{=}CH_2$), allyl ($-CH_2CH{=}CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\ CH_2CH_2CH_2CH{=}CH_2$).

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. Examples include, but are not limited to: acetylenic ($-C{\equiv}CH$) and propargyl ($-CH_2C{\equiv}CH$),

The terms "alkylene" and "alkyldiyl" each refer to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene ($-CH_2-$) 1,2-ethyl ($-CH_2CH_2-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene, i.e. double carbon-carbon bond moiety. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne, i.e. triple carbon-carbon bond moiety. Typical alkynylene radicals include, but are not limited to: acetylene ($-C\equiv C-$), propargyl ($-CH_2C\equiv C-$), and 4-pentynyl ($-CH_2CH_2CH_2C\equiv CH-$).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Heteroaryl" means a monovalent aromatic radical of one or more carbon atoms and one or more atoms selected from N, O, S, or P, derived by the removal of one hydrogen atom from a single atom of a parent aromatic ring system. Heteroaryl groups may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). Heteroaryl bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The heteroaryl group may be bonded to the drug scaffold through a carbon, nitrogen, sulfur, phosphorus or other atom by a stable covalent bond.

Heteroaryl groups include, for example: pyridyl, dihydropyridyl isomers, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl,

naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

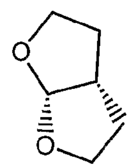
Substituted substituents such as "substituted alkyl", "substituted aryl", "substituted heteroaryl" and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" means a saturated, unsaturated or aromatic ring system including at least one N, O, S, or P. Heterocycle thus include heteroaryl groups. Heterocycle as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A. "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; Katritzky, Alan R., Rees, C.W. and Scriven, E. "Comprehensive Heterocyclic Chemistry" (Pergamon Press, 1996); and *J. Am. Chem. Soc.* (1960) 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl,

isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

One embodiment of the bis-tetrahydrofuranyl group is:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring system having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to

12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl. Carbocycle thus includes some aryl groups.

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a phosphonate group to a drug, or between the Formula I scaffold and substituents. Linkers include L interposed between Ar and the nitrogen of Formula I compounds. Linkers may also be interposed between a phosphorus containing A^3 group and the R^1, R^2, R^3, R^4, R^5, R^6 or R^7 positions of Formula I. Linkers include, but are not limited to moieties such as O, S, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6. Linkers also include repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

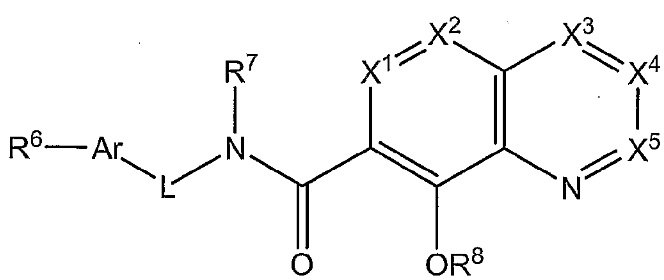
"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds

(1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

AZA-QUINOLINOL PHOSPHONATE COMPOUNDS

Novel aza-quinolinol phosphonate compounds with inhibitory activity against HIV integrase are described, as embodied in Formula I, including any pharmaceutically acceptable salts thereof. In one aspect, the compounds include an active form for inhibition of nuclear integration of reverse-transcribed HIV DNA.



I

Ring atoms, X^1, X^2, X^3, X^4 and X^5 are independently selected from nitrogen (N), substituted N, or substituted carbon.

The compounds of the invention include all enol and tautomeric resonance isomer forms of Formula I. Formula I includes compounds wherein:

X^1 is CR^1, NR, or N;

X^2 is CR^2, NR, or N;

X^3 is CR^3, NR, or N;

X^4 is CR^4, NR, or N;

X^5 is CR^5, NR, or N;

At least one of X^1, X^2, X^3, X^4, and X^5 is NR or N.

Exemplary structures within Formula I include the following: